Ratchet-like genetic mutations make evolution irreversible

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Joe Thornton has found that evolution's backward is blocked by mutations. Credit: University of Oregon

(PhysOrg.com) -- A University of Oregon research team has found that evolution can never go backwards, because the paths to the genes once present in our ancestors are forever blocked. The findings -- the result of the first rigorous study of reverse evolution at the molecular level -- appear in the Sept. 24 issue of *Nature*.

The team used computational reconstruction of ancestral gene sequences, DNA synthesis, protein engineering and X-ray crystallography to resurrect and manipulate the gene for a key hormone

receptor as it existed in our earliest vertebrate ancestors more than 400 million years ago. They found that over a rapid period of time, five random mutations made subtle modifications in the protein's structure that were utterly incompatible with the receptor's primordial form.

The discovery of evolutionary bridge burning implies that today's versions of life on Earth may be neither ideal nor inevitable, said Joe Thornton, a professor in the UO's Center for Ecology and Evolutionary Biology and the Howard Hughes Medical Institute.

"Evolutionary biologists have long been fascinated by whether evolution can go backwards," Thornton said, "but the issue has remained unresolved because we seldom know exactly what features our ancestors had, or the mechanisms by which they evolved into their modern forms. We solved those problems by studying the problem at the molecular level, where we can resurrect ancestral proteins as they existed long ago and use molecular manipulations to dissect the evolutionary process in both forward and reverse directions."

Thornton's team, which included UO research scientist Jamie Bridgham and collaborator Eric A. Ortlund, a biochemist at Atlanta's Emory University, focused on the evolution of a protein called the glucocorticoid receptor (GR), which binds the hormone cortisol and regulates the stress response, immunity, metabolism and behavior in humans and other vertebrates.

"This fascinating study highlights the value of studying evolutionary processes," said Irene Eckstrand, who oversees evolution grants at the National Institutes of Health's National Institute of General Medical Sciences. "By showing how molecular structures are finely tuned by evolution, Dr. Thornton's research will have a broad impact on basic and applied sciences, including the design of drugs that target specific proteins."

In previous work, Thornton's group showed that the first GR evolved more than 400 millions ago from an ancestral protein that was also sensitive to the hormone aldosterone. They then identified seven ancient mutations that together caused the receptor to evolve its new specificity for cortisol.

Once Thornton's team knew how the GR's modern function evolved, they wondered if it could be returned to its ancestral function. So they resurrected the GR as it existed soon after cortisol specificity first evolved -- in the common ancestor of humans and all other vertebrates with bones -- and then reversed the seven key mutations by manipulating its DNA sequence.

'We expected to get a promiscuous receptor just like the GR's ancestor, but instead we got a completely dead, non-functional protein," Thornton said. "Apparently other mutations that occurred during early GR evolution acted as a sort of evolutionary ratchet, rendering the protein unable to tolerate the ancestral features that had existed just a short time earlier."

To identify the mutations, Thornton's team prepared crystals of resurrected ancient GR proteins and took them to the particle accelerator at the Advanced Photon Source outside Chicago, where they used powerful X-rays to determine the protein's atomic structure before and after the shift in function. By comparing the precise atomic maps of each protein, they identified five specific mutations in the later version of the GR that clashed with the architecture of the earlier protein.

"Suppose you're redecorating your bedroom -- first you move the bed, then you put the dresser where the bed used to be," Thornton said. "If you decide you want to move the bed back, you can't do it unless you get that dresser out of the way first. The restrictive mutations in the GR prevented evolutionary reversal in the same way."

When Thornton's group set the five mutations back to their ancestral state, the protein could now tolerate having the seven key changes reversed, which then transformed it into a promiscuous receptor just like the its ancestor.

Despite their powerful role as a ratchet preventing reversal, the five restrictive mutations had little or no direct effect on the protein's function when they occurred. And although they must be reversed before the protein can tolerate the ancestral state, reversing them first does absolutely nothing to enhance the ancestral function. "This means that even if the ancestral function were suddenly to become optimal again, there's no way natural selection could drive the protein directly back to its ancestral form," Thornton said.

GR's evolutionary irreversibility suggests that the molecules that drive our biology today may not be inevitable products of the evolutionary process. "In the GR's case, restrictive mutations erased the conditions that previously opened up the ancestral form as an evolutionary possibility. It's likely that throughout history other kinds of restrictive mutations have taken place, closing off innumerable trajectories that evolution might otherwise have taken," Thornton speculated.

"If we could wind back the clock and allow history to unfold again, different sets of mutations, apparently inconsequential at the time, would almost certainly occur, opening up some potential paths and blocking others -- including the one that leads to the present that actually evolved in our world," he said. "If what we observed in GR evolution is a general phenomenon, then the biology we have is just one of many possible rolls of the evolutionary dice."

Source: University of Oregon (news : web)